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Lithium-induced context aversion in rats as a model of anticipatory nausea in humans

Marcial Rodriguez[a], Matias Lopez[a], Michelle Symonds[b], Geoffrey Hall[b,*]

[a]*Department of Psychology, University of Oviedo, 33003 Oviedo, Spain*
[b]*Department of Psychology, University of York, York YO10 5DD, UK*

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Abstract

In three experiments, rats received injections of lithium chloride (LiCl) before being exposed to a distinctive context. In a subsequent test, rats given access to sucrose solution in this context consumed less than control subjects given sucrose in another context that had been paired with a saline injection (Experiment 1), or was quite novel (Experiment 2). Experiment 3 demonstrated that a context that had been associated with LiCl would serve to block the acquisition of a conditioned flavor aversion when it was presented immediately after the injection on a flavor–LiCl trial. These results show that a procedure in which rats experience the adverse effects of a lithium injection in the presence of contextual cues is effective in endowing those cues with aversive properties. It is argued that the context evokes a state of conditioned nausea, and the parallel with the clinical phenomenon of anticipatory nausea and vomiting (ANV) in human patients is outlined.

Keywords: Context; Aversion conditioning; Nausea; Rats

Anticipatory nausea and vomiting (ANV) can be a distressing side effect of cancer chemotherapy — after a few sessions of treatment (the infusion of cytotoxic drugs), the patient may find that the cues that distinguish the clinic, its sights, sounds, and smells, are capable of evoking nausea and vomiting [1]. This effect has been interpreted as being an instance of classical conditioning in which the set of cues that constitutes the clinic functions as a conditioned stimulus (CS), with the state evoked by the drug infusion serving as the unconditioned stimulus (US). The clinic thus comes to evoke the complex conditioned response (CR) that is nausea and vomiting (e.g., Refs. [10,25]). This analysis has prompted the suggestion that it might be possible to use the procedures of the conditioning laboratory to develop a useful animal model of ANV (e.g., Refs. [17,21]). Attention has focused on the effects produced in rats by the administration of a nausea-inducing agent (usually an injection of lithium chloride (LiCl)) in association with a particular set of contextual cues.

There is plentiful evidence to show that pairing contextual cues with the effects of a lithium injection will endow the context with conditioned properties. A variety of different CRs have been assessed. They include suppressed consumption of (otherwise palatable) fluids in the presence of the contextual cues (e.g., Refs. [4,7,9]); blocking of the acquisition of a conditioned flavor aversion by presentation of the context in compound with the flavor on conditioning trials (e.g., Refs. [7,26,27,29]); the tendency to avoid locations associated with LiCl on a place-preference test (e.g., Ref. [4,5]); and finally, it has been demonstrated that the direct response to contextual cues is changed when the context has been paired with a lithium injection — most notably, general activity tends to be suppressed (e.g., Ref. [20]). It remains to be established, however, that either the training procedures or the response measures used in these experiments provide an appropriate parallel to the phenomenon of ANV.

First, with respect to the response measure, the essence of the conditioning account of ANV is that the contextual cues

* Corresponding author. Tel.: +44-1904-433-144; fax: +44-1904-433-181.

E-mail address: gh1@york.ac.uk (G. Hall).

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(the cues of the clinic) must be assumed to evoke a conditioned state of nausea. Measurement of such a state in animal subjects (especially for a species like the rat that does not vomit) must necessarily be indirect, and there may be debate over whether the CRs described in the previous paragraph accurately reflect the presence of nausea conditioned to contextual cues. Some authors (e.g., Ref. [4]) have drawn attention to the complexity of the event used as the US used in these experiments — in particular, an injection of LiCl will be aversive in more than one way, producing not only the state of sickness but also, in some cases, somatic pain. It has also been suggested that associations will be formed preferentially between exteroceptive (e.g., contextual cues) and pain, and will not form between these cues and sickness (e.g., Refs. [14,15]). It is possible then that the CRs evoked in the rat by a lithium-associated context indicate the state evoked by a CS that has signaled a painful US rather than the state of conditioned sickness. In the case of the conditioned place avoidance test, there is direct experimental evidence [4,18] that this response is sensitive to the capacity of the injection to evoke pain rather than to any sickness that the injection evokes.

Direct observations of the behavior shown in the context do not strongly support the view that the context can come to elicit a state of conditioned nausea. A suppression of general activity is an aspect of the unconditioned response (UR) to a lithium injection, and as we have already noted, is also seen as a CR. However, the nature of this suppression differs in the two cases [20] — the UR consists chiefly of the pattern known as lying-on-belly (in which there is a loss of muscle tone, and the animal lies with its head slumped to the cage floor), whereas the CR consists of a freezing response (in which the head and body are held rigid). The UR has been taken to reflect a state of sickness, and although they cannot prove the point (these different patterns of behavior could reflect the animal's response to different degrees of the same state), these observations raise doubts about the proposal that the CR evoked by a context is a state similar to that evoked by the US itself. They are consistent with the alternative possibility that contextual cues, by virtue of the fact that they have signaled the imminent occurrence of a distressing episode, acquire the power to evoke a state of anxiety, which reveals itself in the conditioned emotional response of freezing.

A further problem for the proposed animal model of ANV is that the training procedures typically employed in the animal experiment map rather poorly onto the procedures used for patients in the clinic. Patients are given the therapeutic-drug infusion shortly after entering the clinic, and the nausea it generates is experienced in the presence of the contextual cues. With a few exceptions (e.g., Refs. [2,6]), the majority of the animal studies have used a standard forward-conditioning procedure in which the rats are given an initial period of exposure to the context (the CS) followed by an injection of LiCl (the US) that immediately precedes return to the home cage. In order to develop the animal model, therefore, it is important to determine if rats can acquire context aversions when the injection occurs prior to their being given exposure to the target context. It is possible that the effective US with this procedure will be the state of nausea produced by the injection, and this state will take time to develop. Parker et al. [24] monitored the time course of the behavioral effects produced in rats by a dose of lithium. They noted that the behavior pattern lying-on-belly showed a gradual increase reaching a peak 15 min after the injection and then decreased, ceasing at about 30 min after the injection. If the state indexed by this behavior is the effective US, then a conditioning procedure in which the injection is given prior to placement in the context should ensure that the rat experiences the CS and the US concurrently if it is exposed to the context for 15–30 min following the injection. Excitatory conditioning might thus be expected to occur.

Evidence that excitatory conditioning can occur with this training procedure comes from studies using the conditioned place avoidance test (e.g., Ref. [22]) or from the direct observations of the rat's response to the context made by Parker et al. [24]. Unfortunately for the attempt to establish an animal model of ANV, it is just these CRs that were identified in our earlier discussion as being untrustworthy as measures of a state of conditioned sickness. What is needed if the model is to be taken further is a clear demonstration that this conditioning procedure is effective in producing conditioning with a CR that can be identified more confidently with the state of conditioned sickness. The experiments reported here attempt to do this making use of the suppression-of-consumption measure in Experiments 1 and 2 and a blocking test in Experiment 3.

1. Experiment 1

All animals in this experiment received training in which they were exposed to two distinctive contexts (novel cages, each different from the home cage). One context (Context A) was experienced after the rats had been given an injection of LiCl; an injection of saline preceded experience of Context B. We assume that excitatory conditioning will be best achieved with this training procedure when the animals experience the full effects of the injection in the presence of the contextual cues. On the basis of the observations made by Parker et al. [24] described earlier, we decided to move the animals to the training contexts immediately after the injection had been given and to leave them there for 30 min before returning them to their home cages.

The animals were divided into two groups for the test phase (see Table 1). The experimental group received access to a sucrose solution in Context A and the control group received access to sucrose in Context B. If this procedure generates the same effect as that in which the lithium injection follows context exposure (e.g., Refs. [7–9]), we

Table 1
Experimental designs and results

Experiment 1			
Group	Training	Test (ml sucrose consumed)	
Experimental	Li → A and Sal → B	A: 12.0 (0.70)	
Control	Li → A and Sal → B	B: 16.2 (0.99)	
Experiment 2			
		Test (ml sucrose consumed)	
Group	Training	Trial 1	Trial 2
Conditioned	Li → A	A: 12.9 (0.71)	A: 14.0 (0.83)
Novel	Li → A	B: 14.6 (1.14)	B: 17.0 (0.95)
Experiment 3			
Group	Context conditioning	Compound conditioning	Test (ml sucrose consumed in home cage)
Blocking	Li → A and B	Suc → Li → A	8.6 (1.73)
Control	Li → A and B	Suc → Li → B	1.9 (0.45)

A and B refer to different distinctive contexts, Li and Sal refer to injections of LiCl and saline given just before the rats were put into the contexts, Suc refers to access to a sucrose solution, and scores are group means (standard errors in parentheses).

may expect to find that the first group consumes less than the second. It is known that one direct effect of an injection of LiCl is to produce a suppression of consumption of flavored solutions [12], and this behavior can be taken to be one of the ways in which rats exhibit the state of nausea. To this extent, a demonstration that conditioned contextual cues can come to elicit the same sort of response would encourage the conclusion that these cues evoke a state of conditioned nausea.

An important feature of the procedure used in this experiment is that the rats were not given access to food or drink during the context-conditioning trials. In most previous studies of context aversion learning, it has been customary to allow access to a flavored fluid (e.g., Ref. [7]) or to plain water (e.g., Ref. [9]) during conditioning. A possible consequence of this procedure is that the animals might acquire an (context-specific) aversion to the fluid consumed during training. Suppression of consumption in the test phase might then represent not an aversion to the context itself but generalization of the flavor aversion formed during training (see Refs. [26,29]). Our present procedure eliminates this possible confound.

1.1. Method

1.1.1. Subjects and apparatus

The subjects were 16 male hooded (Lister) rats with a mean free-feeding body weight of 342 g (range: 360–320 g). They were housed singly in home cages made of opaque white plastic measuring $35 \times 22 \times 19$ cm. These had a roof of wire mesh that held food and (when available) a water bottle, and a layer of wood shavings covered the floor. The home cages were kept in a colony room that was brightly lit from 8:00 to 20:00 h each day. The rats were maintained on a water-deprivation schedule (described below) but were allowed continuous access to food throughout the experiment.

Two further sets of cages, both different from the home cages and located in separate parts of the laboratory, served as the experimental contexts. One set of cages was located in a small room dimly lit by a single 60-W red lamp. The cages were made of transparent plastic, and measured $36 \times 20 \times 20$ cm. The floors of these cages were covered with commercially obtained cat litter, and the roof was made of wire mesh with a hole through which a drinking spout could be inserted. A speaker supplied a constant background white noise with an intensity of 75 dB measured next to the cages. The cages that constituted the other context were larger, measuring $42 \times 35 \times 16$ cm, and were located in a brightly lit colony room. The walls and floor of the cage were made of translucent white plastic, and the roof of wire mesh. These two sets of cages are known to be discriminably different from each other having been used in our previous studies of context conditioning (e.g., Ref. [26]). Calibrated tubes equipped with stainless steel ball-bearing-tipped spouts were used to present measured quantities of a 3.4% sucrose solution in these cages during the test phase. Fluid consumption was measured by weighing the tubes before and after fluid presentation and recording to the nearest 0.5 g. The US for the conditioning trials was an injection of 0.15-M LiCl administered intraperitoneally at 20 ml/kg of body weight.

1.1.2. Procedure

For the initial stage of water deprivation, the rats remained in their home cages. During this period, they were given access to water presented in the plastic drinking tubes, for two daily 30-min sessions, initiated at 10:00 and 17:00 h. Presentations of water continued to be given at these times throughout the conditioning phase. The subjects were

assigned to two equal-sized groups approximately matched in terms of the amount of water they consumed in this stage.

The next 8 days constituted the conditioning phase. On Day 1, all subjects were removed from their home cages at 12:30 h, given an injection of LiCl, and then transferred to Context A where they remained for 30 min before being returned to their home cages. On Day 2, the same procedure was followed except that the injection was of saline (0.15 M at 20 ml/kg of body weight), and this preceded 30 min spent in Context B. This 2-day cycle was repeated a further three times. For half the animals in each group, the larger cages served as Context A and the smaller as Context B; for the remaining animals, the assignment was reversed. It was noted that the amount of water consumed in the home cage tended to decline over the 8 days of conditioning. Accordingly, the conditioning phase was followed by a recovery period of 4 days in which the subjects remained in their home cages receiving the usual access to water for 30 min at 10:00 and 17:00 h.

On the next day, all animals received a presentation of 20 ml of the sucrose solution in the home cage at 12:30 h for 30 min in order to familiarize them with the flavor to be used on test. Supplementary water was given to the subjects in their home cages for 30 min at 17:00 h. The single test session occurred on the following day. At 12:30 h, the animals were transferred to one of the experimental contexts; Context A for the experimental group and Context B for the control group. There they received access to the sucrose solution for 15 min.

1.2. Results and discussion

No data were recorded during the conditioning phase of the experiment. The groups did not differ in the amount of sucrose solution they consumed on the familiarization session: 13.5 ml for the experimental group and 14.3 ml for the control group ($F<1$). The data of central interest, those for the test in which sucrose was presented in the contexts, are given in Table 1. They show that the experimental group (tested in Context A) consumed less than the control group (tested in Context B). An analysis of variance (ANOVA) showed the difference between the groups to be statistically reliable, $F(1,14)=12.26$, $P=.003$. (The rejection criterion adopted for this and all subsequent analyses was $P<.05$.) Thus, just as has been previously shown for the case in which the injection follows context exposure, this experiment shows that consumption is suppressed by a context experienced immediately after an injection of LiCl. This result is consistent with the proposal that the context has acquired aversive properties, and in particular, can come to evoke a state of conditioned nausea. The validity of this interpretation will be assessed in Experiments 2 and 3.

Suppression of sucrose consumption was obtained in this experiment in the experimental group in spite of the fact that fluid consumption was not possible during the conditioning trials. In a previous study (Experiment 1 in Ref. [29]), we found evidence of a suppression of consumption on test only in animals that were given a fluid to drink in the context during the conditioning phase. This result led us to the conclusion that generalization of a flavor aversion formed during conditioning might make an important contribution to the outcome of a consumption test. Clearly, such generalization cannot be responsible for the result observed here. It remains to explain, however, why the consumption test proved sensitive to the effects of context conditioning in this experiment but failed to show an effect for animals trained under approximately equivalent conditions in the experiment by Symonds et al. [29]. The chief difference between the experiments was that Symonds et al. [29] used a forward-conditioning procedure in which exposure to the context was followed by the injection of LiCl. This prompts the speculation that perhaps the present procedure (in which the effects of the injection are likely to be experienced in the presence of the contextual cues) produces a more powerful context aversion than does the standard procedure in which exposure to the context occurs prior to the LiCl injection. If so, then it may be possible to obtain a result on a consumption test even in the absence of any contribution from the generalization of an aversion formed to the fluid consumed during conditioning.

Our success, in this experiment, in obtaining evidence of a context aversion in animals that were not permitted to eat or drink in the context during the conditioning phase prompts two further observations. First, it provides a further reason to reject the suggestion (e.g., Ref. [13]) that ingestion is necessary for a context–illness association to be formed (see also Ref. [29]). In this respect at least, the conditions governing the formation of such associations appear to be no different from those governing classical conditioning generally. Second, it lends support to the proposal that context conditioning might provide a useful animal model of ANV. There is no reason to suppose that ANV will develop only in patients who are allowed to eat or drink in the clinic during treatment, and it is thus important to be sure that context aversion learning in the rat is not constrained by such a requirement.

2. Experiment 2

As we have already noted, Parker et al. (Experiment 4 in Ref. [24]) recorded the behavior displayed by rats in the 30-min period following an injection of LiCl. The chief effect of the injection was to induce the behavior patterns referred to as lying-on-belly and body drag (the rat stretches out and drags its belly along the cage floor) and to produce a suppression of the behaviors usually seen in a novel context — locomotion, rearing, and grooming. A rat that experiences a novel context in these conditions does not conduct, in full measure, the exploratory behavior by which a rat normally familiarizes itself with the context. In

the experiment just reported, therefore, it is possible that, by the end of training, the rats were differentially familiar with the two contexts — although they had spent the same amount of time in Contexts A and B, the state evoked by the injection given prior to exposure to Context A might have reduced the extent to which they explored that context. This, in itself, could be enough to explain the results obtained. Animals tested in Context A may have experienced a set of cues that were still, to some extent, novel. This could produce a suppression of consumption, perhaps because neophobia to the test fluid is enhanced in a novel context, or simply as a result of response competition — a tendency to explore the context could use up time that would otherwise be spent drinking. In either case, there would be no need to assume that an association had been formed between the context and a state of nausea induced by the lithium injection.

The present experiment was designed to evaluate the possibility that the suppressed consumption observed in the conditioned context is a consequence of the rat's reaction to the novelty of the context. There were two groups of subjects (conditioned and novel groups). During the training phase, both groups experienced Context A under the effects of LiCl; Context B was not used in this stage. In the test, the conditioned group was given access to sucrose in Context A, whereas the novel group was given sucrose in Context B (see Table 1, center panel). If suppression of consumption is determined solely by the novelty of the test context, then the effect should be particularly marked in the novel group. But if the suppression shown by the conditioned group is as great or greater than that shown by the novel group, we may conclude that some other factor (the conditioned properties of the test context) plays a role.

2.1. Method

The subjects were 32 male hooded (Lister) rats with a mean free-feeding weight of 379 g (range: 460–325 g). They had previously served as subjects in an experiment using an appetitive-conditioning procedure, but were naive to all aspects of the current stimuli and procedures. Except where otherwise stated, apparatus, experimental contexts, and other procedural details were the same as those in Experiment 1.

As in the previous experiment, conditioning began just after the water-deprivation schedule had been established. All animals received four conditioning trials in which they were injected with the LiCl just before being put into Context A. Each conditioning trial was followed by a rest day on which the animals remained in their home cages. Thus, as in Experiment 1, the conditioning phase lasted 8 days. On Day 9, the sucrose familiarization session was given. There were two test sessions given on Days 10 and 11. On each session, the sucrose solution was made available for 30 min in Context A for the conditioned group and in Context B for the novel group.

2.2. Results and discussion

On the sucrose familiarization session, the conditioned group drank 14.1 ml and the novel group drank 14.4 ml ($F < 1$). Table 1 shows group mean sucrose consumption for the two test sessions. Levels of consumption were somewhat higher on Test 2 than on Test 1, but on both, the novel group drank more than the conditioned group. An ANOVA with group and test session as the variables was conducted on the data summarized in Table 1. This analysis revealed a significant effect of group, $F(1,30) = 4.27$, $P = .047$, and a significant effect of session, $F(1,30) = 9.77$, $P = .003$. The interaction between these two variables was not significant, $F(1,30) = 1.36$.

These results confirm those of Experiment 1 in showing that consumption is suppressed in a context that has been associated with a lithium injection compared with the level shown in a control context that has not been associated with lithium. The new finding is that this difference is evident when the control context is novel. That the difference was not as marked in this experiment as in the previous studies may well reflect the fact that a novel test context is likely to evoke exploratory responses that would compete with drinking behavior. But that a difference is nonetheless found rules out the suggestion that the suppression shown in the conditioned group is solely an artifact of their response to novel aspects of that context — even if exposure to the context under the influence of a lithium injection restricts exploration, the test context for the conditioned group will still be somewhat more familiar than the test context used for the novel group. We conclude that the performance of the conditioned group depends on the conditioned aversive properties of the context.

What remains to be established, however, is the exact nature of the CR that comes to be evoked by this conditioning procedure. Our results are consistent with the suggestion that contextual cues evoke a state of conditioned nausea; but there is, as we have already acknowledged, an alternative possibility. If the contextual cues acquire the power to evoke a state of anxiety (because they have been associated with an aversive event), the consequent conditioned emotional response could be enough to interfere with fluid consumption. To demonstrate that the context evokes nausea requires a different test procedure. This issue is taken up in Experiment 3.

3. Experiment 3

It is generally accepted that the avoidance of a flavor that has previously been paired with illness reflects the acquisition, in some measure, of nausea-inducing properties by the flavor. One line of evidence to support this view comes from studies of the effects of drugs used as anti-emetics in humans, showing that these drugs can attenuate the expression of a conditioned taste aversion

(e.g., Refs. [3,11,16]). There is, as yet, little comparable evidence for the case of context aversion learning (although a recent study by Symonds and Hall [28] has shown that the anti-emetic ondansetron can prevent the acquisition of a context aversion).

A second line of evidence applied to the case of flavor aversion learning depends on making a comparison between the response evoked as a UR by the illness-inducing procedure (e.g., a lithium injection) and that evoked as a CS by the flavor (e.g., Ref. [20,23]). The similarity of the UR and the CR supports the proposal that both reflect the same state. Thus, Meachum and Bernstein [19] gave rats intraoral presentations of flavors that previously had been paired with LiCl, and observed that the same patterns of behavior (e.g., lying-on-belly) were produced by the flavors as were elicited by the administration of LiCl itself. We have already argued for the case of context conditioning, that the suppression of consumption evoked by a lithium-associated context might be taken to indicate the presence of a state of (conditioned) nausea, as this same reaction is seen after an injection of LiCl itself (i.e., forms part of the UR). Other features of the comparison between the UR and the CR evoked by a context CS are less encouraging for this conclusion. As we noted earlier, Meachum and Bernstein [20] found that the CR of immobility in the presence of context cues consisted of a freezing response and not the lying-on-belly pattern. Such freezing is consistent with the suggestion that the conditioning procedure has endowed the context with the ability to evoke a state of anxiety. Suppression of fluid consumption could thus be a consequence of the presence of this state rather than of a state of nausea.

In order to address this issue, Experiment 3 made use of a two-stage conditioning design to assess the extent to which conditioned contextual cues might block the acquisition of a flavor aversion trained in their presence (see Table 1). After a context-conditioning phase similar to that used in Experiment 1, the animals received a compound-conditioning trial in which both contextual cues and a novel flavor were associated with a lithium injection. On this trial, consumption of a sucrose solution (presented in the home cage) was followed by an injection of LiCl after which the animals were transferred to one of the experimental contexts. For half of the subjects (blocking group), this was Context A (the context previously paired with LiCl); for the remainder (control group), Context B was used. We anticipated (see Ref. [26]) that the presence of the previously conditioned, Context A, cues would block acquisition of an aversion by sucrose so that subjects in the blocking group would consume this flavor relatively readily on a subsequent test trial. This result would provide evidence that pairing a context with a lithium injection can endow that context with nausea-evoking properties.

The argument to support this interpretation runs as follows. We may suppose that blocking occurs when a US representation, that is normally effective in forming an association with the target CS, is unable to do so if this representation has been associatively activated by the presence of the pretrained CS. According to this analysis, in order to produce blocking, the pretrained CS needs to activate those aspects of the US representation that would otherwise enter into association with the target CS. Thus, if a context that has previously been associated with a lithium injection blocks the development of a flavor aversion with lithium as the US, we may conclude that the context is able to activate that aspect of the US that is responsible for flavor aversion learning. And if it is accepted that flavor aversion depends on an association between the flavor and nausea, blocking by context would constitute evidence that the initial phase of training had established a context–nausea association. If the contextual cues merely evoke a state of anxiety, there is no reason to think that they will block the formation of an association between the flavor and that aspect of the US representation that produces the state of nausea.

3.1. Method

The subjects were 16 male hooded (Lister) rats with a mean free-feeding weight of 366 g (range: 425–330 g). They had a similar experimental history and were maintained in the same way as the subjects in Experiment 2. They were naive with respect to the current stimuli and procedures.

The subjects were water-deprived, divided into equal-sized blocking and control groups, and then given a context-conditioning treatment similar to that described for the subjects in Experiment 1. Thus, over the course of 8 days, they experienced Context A four times and Context B four times; an injection of LiCl preceded each experience of Context A. The saline injection prior to experience of Context B was not used in this study — unpublished experiments from our laboratory have shown that the context-conditioning effect of Experiment 1 can be obtained whether such injections are given or not.

On the single compound-conditioning trial, all subjects received access to 20 ml of sucrose in their home cages for 30 min, followed immediately by an injection of LiCl. Subjects in the blocking group were then transferred to Context A for 30 min; subjects in the control group spent 30 min in Context B. After a recovery day on which the subjects received two 30-min sessions of free access to water in the home cages (at 10:00 and 17:00 h), a single test trial was given in which subjects were given a 30-min presentation of sucrose in the home cages at 12:30 h. Other procedural details were identical to those described for the previous experiments.

3.2. Results and discussion

On the compound-conditioning trial, in which sucrose was presented in the home cage, the blocking group consumed somewhat more than did the control group (the group mean scores were 16.7 and 13.7 ml, respectively).

These scores did not differ reliably, $F(1,14) = 3.09$. Consumption in both groups was reduced on the test trial (see the lower panel of Table 1), and on this trial, the blocking group drank significantly more than the control group, $F(1,14) = 13.9$, $P = .002$. This outcome suggests that Context A had acquired aversive properties in the first stage of training, and was thus able to block the acquisition of an aversion to the sucrose. This general result is not, in itself, novel — blocking of flavor aversion learning by contextual cues has been demonstrated several times before (e.g., Refs. [7,26,30,31]). In these earlier experiments, however, the initial context aversion was established by the standard forward-pairing procedure in which exposure to the context preceded the injection. It was thus necessary for us to demonstrate that the blocking effect could be obtained with the particular, backward-pairing, procedure employed in our other experiments.

We have argued that blocking occurs when different cues are in competition for association with a given US representation. If it is accepted that flavor aversion depends on a flavor–nausea association, then, since a pretrained context can block this learning, it follows that the pretraining must have established a context–nausea association. Best et al. [6] have advanced an analogous argument with respect to second-order conditioning in an investigation of the properties acquired by contextual cues that had been associated with an injection producing gastric malaise. They demonstrated that rats given access to a novel flavor and then placed in the conditioned context would develop an aversion to the flavor, and concluded that the contextual cues had become capable of evoking "learned sickness" (Ref. [6], p. 256). It is true that the nausea-inducing agent employed by Best et al. [6] was an injection of apomorphine, but similar second-order conditioning effects have been reported by Archer and Sjödén [2] in a study that used a lithium injection as in the present experiments.

4. General discussion

In all the experiments reported here, rats were given an injection of LiCl before being put into a distinctive context. At an operational level, this procedure can be construed as involving backward conditioning in that the US (the injection) occurs before the putative CS (the context) is experienced. It takes several minutes, however, for the effects of an injection of LiCl to become fully evident, which means that this procedure should ensure that any nausea produced by the injection would be preceded by and experienced in the presence of the contextual cues. If the state of nausea is the effective US, then excitatory conditioning might be expected to occur, with the context acquiring conditioned aversive properties. Our results showed evidence of such conditioning. Consumption of an otherwise readily accepted substance was suppressed in the presence of conditioned contextual cues (comparison being made both with the level of consumption shown in a familiar but unconditioned context, and with that shown in a novel context). More critically, for the argument that contextual cues can come to evoke a state of conditioned nausea, it was also shown that such cues were effective in blocking the acquisition of a flavor aversion when flavor and context were trained in compound.

These results prompt a number of conclusions. First, it is worth noting that the procedure used in the present set of experiments appears to provide a more sensitive measure of contextual conditioning than those previously employed. There is a substantial body of evidence in the literature, which, in contrast to the procedure used in the present studies, demonstrates contextual conditioning by means of a training procedure in which subjects are given exposure to the target context prior to receiving an injection of LiCl (e.g., Refs. [9,21,30]). As with the present procedure, evidence for an aversion to the context is then revealed in a subsequent test in which the subjects decline to consume an otherwise palatable flavor when placed in the target context. One problem inherent in this procedure, however, comes from the observation that the conditioning effect is sometimes enhanced in subjects who have had an opportunity to consume a flavor on the conditioning trials (e.g., Refs. [9,21]), and in some cases, is not evident at all if a fluid is not made available during pretraining [29]. This has led to the proposal that context aversion learning does not obey the same rules that govern other instances of classical conditioning, since its development is aided by the presence of another cue at the time of conditioning. It is likely, however (see Ref. [27] for a discussion), that the use of a consumption test to measure contextual aversions is contaminated, to some extent, by generalization to the test flavor of any aversion formed to the fluids presented during the conditioning phase. No such problem arises in the present study — subjects receive no access to fluids of any sort during the conditioning phase, and so we can assume in this case that the consumption test used in Experiments 1 and 2 provides a valid measure of contextual conditioning. That an aversion can be demonstrated under these conditions implies that the procedure must have been particularly effective in endowing the contextual cues with associative strength.

The second issue to arise from these findings, and the one which forms the main focus of the present paper, is whether the procedure developed in these experiments can be regarded as a good candidate for an animal model of the conditioned side effects experienced by cancer patients undergoing chemotherapy. The present procedure has two main properties, which give it rather more practical validity than previous techniques used to measure context aversions. First, as with patients given therapeutic drugs in the clinic, our procedure should ensure that the effective US is experienced in the presence of the relevant cues. And secondly, as we have noted above, the present procedure arranges that no fluids are made available during the

context-conditioning trials (there is no suggestion that patients are required to consume a fluid prior to drug treatment in order to develop the anticipatory nausea response). Our observations, from both consumption and blocking tests establish that conditioning occurs with this procedure — what is now needed, if the clinical relevance of our procedure is to be taken further, is to determine the exact form of the CR.

As Meachum and Bernstein [20] have noted, chemotherapy patients who have experienced drug-induced nausea in the presence of a certain set of contextual cues report that these cues themselves become capable of evoking nausea. Do rats that have experienced the effects of a lithium injection in a given context similarly develop a CR of nausea to the contextual cues? An alternative view might be to suppose that animals decline to consume the test fluid in the target context not because it evokes a state of nausea, but because it simply predicts the onset of illness. Evidence relevant to this question comes from comparing the form of the CR with that of the UR elicited by the lithium injection itself. In some respects, these differ — the characteristic lying-on-belly component of the UR is not seen in the CR; but, as we have already said, this difference may simply indicate a difference in the intensity of the nausea evoked by the CS and the US. In other respects, the CR and the UR appear to be similar — pilot work conducted in this laboratory, using the same stimuli and procedures as those employed in the present experiment, has confirmed that one UR to an injection of LiCl is a refusal to consume otherwise palatable fluids, and this same response is shown in the presence of conditioned contextual cues (Experiments 1 and 2). Such cues will also block the acquisition of a conditioned flavor aversion (Experiment 3), implying that they are capable of eliciting the state of nausea that is generally assumed to be the effective US in such learning. And more recently, we have conducted a further study in this laboratory using the present experimental paradigm, which shows that the administration of an anti-emetic prior to testing will reduce the magnitude of the CR that is displayed in the conditioned context. The balance of the evidence is thus probably enough to merit the conclusion that for the rats in our experiments, as for the patients in the chemotherapy clinic, contextual cues can acquire the power to elicit a CR of nausea. This encourages us to pursue the present experimental paradigm as a possible starting point in the development of an animal model of ANV with the intention of exploring procedures that might restrict the acquisition of context aversions and that might be capable of transfer to the clinic as interventions for the alleviation of such conditioned side effects.

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